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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,435	02/15/2002	M. Vijay Kumar	M0351-268908	3474

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,435	KUMAR, M. VIJAY	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *1-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/21/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claims 45-52, which are related to claims 28-44 and are not new matter.

Accordingly, claims 28-52 are examined in the instant application.

The following are the remaining rejections.

This application contains claims drawn to an invention nonelected with traverse in Paper of 09/03/04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

Claims 28-52 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention.

The limitation of the "biological equivalent" of a "wild type"TRAIL polypeptide comprising SEQ ID NO:1 claimed in Claims 28-52 has no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for a TRAIL polypeptide (Summary, p.3). There is however no mention of the "biological equivalent" of a "wild type"TRAIL polypeptide comprising SEQ ID NO:1.

The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

OBJECTION

1. Claims 28-52 are objected to for the use of the language "biological equivalent". It is not clear what type of biological activity is referred to, nor is it clear what type of equivalent is referred.

2. Claim 50 is objected for the use of the language mitochondrial "function". It is not clear what type of function is referred to.

3. The amendment filed on 01/21/05 is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "a biological equivalent" of the TRAIL polypeptide of SEQ ID NO:1.

Applicant is required to cancel the new matter in the response to this Office action.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art

can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 28-52 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 28-52 are drawn to a composition comprising a "biological equivalent" of a TRAIL polypeptide comprising SEQ ID NO:1, and an antiprogrestin.

Applicant asserts in the response of 01/21/05, on page 15, second paragraph, that biological equivalent of TRAIL polypeptides are those polypeptides that have substitutions, additions, or deletions such that the biological activity is the same, and that such biological equivalent peptides may be evaluated using the assay systems in Examples 2-10.

It is noted that in view of a lack of a definition of a biological equivalent, which encompasses a polypeptide having any of myriads of possible biological activity of SEQ ID NO:1, and in view of a lack of a disclosure of a common structure that confers the biological activity of the claimed biological equivalent, biological equivalents of SEQ ID NO:1 encompass variants of SEQ ID NO:1 with unknown structure.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that □[a] written description of an invention involving a chemical genus, like

a description of a chemical species, □requires a precise definition, such as by structure, formula, [or] chemical name,□ of the claimed subject matter sufficient to distinguish it from other materials.□ Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as □vertebrate insulin cDNA□ or □mammalian insulin cDNA□ without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that □naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.□ Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. □A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.□ Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that □the written description requirement can be met by □show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. □ Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of a biological equivalent of SEQ ID NO:1, as shown in the example of Lilly, by structurally describing a representative number of a biological equivalent of SEQ ID NO:1, or by describing □structural features common to the members of the genus, which features constitute a substantial portion of the genus.□ Alternatively, as shown in the example of Enzo, the specification can show that the claimed invention is complete □by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.□

In this case, the specification does not describe a biological equivalent of SEQ ID NO:1 in a manner that satisfies either the standards as shown in the example of Lilly or

Enzo. The specification does not provide the complete structure of any biological equivalent of SEQ ID NO:1, nor any physical or chemical characteristics of a biological equivalent of SEQ ID NO:1, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single TRAIL polypeptide of SEQ ID NO:1, this does not provide a description of a biological equivalent of SEQ ID NO:1 that would satisfy the standard as shown in the example of Enzo.

The specification also fails to describe a biological equivalent of SEQ ID NO:1 by the example in Lilly. The specification describes only a single TRAIL polypeptide of SEQ ID NO:1. Therefore, it necessarily fails to describe a □representative number□ of such species. In addition, the specification also does not describe □structural features common to the members of the genus, which features constitute a substantial portion of the genus.□

Thus, the specification does not provide an adequate written description of a biological equivalent of SEQ ID NO:1, that is required to practice the claimed invention, and one of skill in the art would reasonably conclude that the specification did not have possession of a biological equivalent of the TRAIL polypeptide of SEQ ID NO:1 at the time the invention was made.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 28-52 are rejected under 112, first paragraph, because while being enabled for the TRAIL polypeptide of SEQ ID NO:1, the specification is not reasonably enabled for "a biological equivalent" of SEQ ID NO:1.

Claims 28-52 are drawn to a composition comprising a "biological equivalent" of a TRAIL polypeptide comprising SEQ ID NO:1, and an antiprogrestin.

Applicant asserts in the response of 01/21/05, on page 15, second paragraph, that biological equivalent of TRAIL polypeptides are those polypeptides that have substitutions, additions, or deletions such that the biological activity is the same, and that such biological equivalent peptides may be evaluated using the assay systems in Examples 2-10.

It is noted that in view of a lack of a definition of a biological equivalent, which encompasses a polypeptide having any of myriads of possible biological activity of SEQ ID NO:1, and in view of a lack of a disclosure of a common structure that confers the biological activity of the claimed biological equivalent, biological equivalents of SEQ ID NO:1 encompass variants of SEQ ID NO:1 with unknown structure.

Applicant has not shown how to make and use the claimed biological equivalents which are capable of functioning or have the properties of the TRAIL polypeptide of SEQ ID NO:1, in view of the unpredictability of protein chemistry, as taught by Bowie et al, Burgess et al, Lazar et al, Tao et al and Gillies et al, all of record.

REJECTION UNDER 35 USC 103

Claims 28-44 remain rejected under 35 USC 103 as being obvious over Bonavida, B et al, 1999, Intl J Oncology, 15(4): 793-802, or Yu et al, 2000, Cancer Res, 60: 2384-2389, IDS # 128, submitted on 11/12/02, or Gliniak B et al, 1999, Cancer Res, 59 (24): 6153-6158, in view of Fathy El Etreby et al, 2000, The Prostate 42: 99-106, IDS # 27, submitted on 11/12/02 or Koide SS et al, J Reproductive Medicine, 1998, 43(7): 551-560, IDS # 53, submitted on 11/12/02, for reasons already of record in paper of 10/21/04.

New claims 45-52 are rejected for the same reasons of record.

Applicant submits a Declaration by Dr. M. V. Kumar, stating the TRAIL polypeptide of the claimed invention is the same as the TRAIL polypeptide of SEQ ID NO:1, as recited in Pitti et al, 1996, JBC, 271: 12687-12690.

Applicant argues that there is no teaching in the cited references of the combination of TRAIL and an antiprogestin, such as Mifepristone, as a chemotherapeutic composition. Applicant argues that although Bonavida teaches a combination of TRAIL with actinomycin D, or cyclohexamide, or adriamycin, each of these agents however function by a completely different mechanisms than TRAIL. Applicant argues that cyclohexamide is a general inhibitor of protein translation, Adriamycin is an antibiotic with antineoplastic activity, and actinomycin D is a transcriptional terminator, that acts by binding to DNA between adjacent G-C pairs. Applicant argues that the use of agents that act by different biochemical pathways is an approach typically employed in combination therapy, which is constrasting with the claimed invention, which employs a combination of two agents that act by the same, or

by very similar biochemical pathways to induce apoptosis. Applicant argues that both Mifespritone and TRAIL act via cell death receptors DR4 and DR5 to stimulate caspase 8, which subsequently activates procaspases 3, 7 and 9, and that Applicant is able to use Mifespristone to sensitize cells to TRAIL by activating the DR4/DR5 pathway. Applicant argues that by constrast the agents proposed by Bonavida act by a much more generalized mechanism to induce cell death, and thus can result in non-specific side effects.

Applicant argues that reading Bonavida, one would be discouraged from using a second agent of the TRAIL pathway in combination with TRAIL, because Bonavida describes using TRAIL with chemotherapeutics that work by different biochemical pathways.

Applicant argues that there is no description in the art to use Mifepristone to induce apoptosis in combination with TRAIL, or that Mifepristone act via the TRAIL pathway. Applicant argues that there is no teaching of using Mifepristone to induce DR5 receptor, and/or caspase processing to thereby induce apoptosis.

The submission of the Declaration by Dr. M V Kumar is acknowledged and entered.

It is noted that Bonavida et al, in their review article, recite Pitti et al, 1996, or reference # 41, in the paragraph describing the properties of TRAIL/APO-2L (page 794, second column, paragraph under TRAIL/APO-2L). Thus the TRAIL polypeptide taught by Bonavida et al encompasses the claimed TRAIL polypeptide of SEQ ID NO:1, which, as confirmed by MPSRCH sequence similarity search, is 100% similar to the full length

polypeptide taught by Pitti et al (MPSRCH search report, 2005, us-10-077-435-1.rup, pages 1-2).

Applicant's arguments of 01/21/05 have been considered but are found not to be persuasive for the following reasons:

It would have been obvious to replace the chemotherapeutic drugs such as actinomycin D, or cyclohexamide, or adriamycin in the combination composition comprising TRAIL polypeptide taught by Fathy El Etreby et al with Mifespristone, because of the following reasons:

1) As pointed out by Applicant, the agents proposed by Bonavida act by a generalized mechanism to induce cell death, and thus can result in non-specific side effects, as compared to specific therapeutic agents,

2) Mifepristone can kill both androgen-sensitive and –insenstive prostate cancer cells, as taught by Fathy El Etreby et al, whereas the art only discloses that TRAIL induces cell death in androgen-independent prostate cancer cells, and thus Mifepristone would be complementary to TRAIL, and

3) Although Mifepristone also kill cancer cells by apoptosis, Mifepristone function by a different mechanism than TRAIL, i.e. Mifepristone is an antiprogestin, i.e. a progesterone receptor antagonist, inhibiting progrestone-dependent processes, wherein the antitumor action by Mifepristone is mediated via the prosgesterone receptor, as taught by Fathy El Etreby et al. In other words, Mifepristone would be complementary to TRAIL.

Further, although the art does not disclose that Mifepristone act via the TRAIL pathway, this is not germane to the above mentioned motivation for combining the references.

In addition, one would have expected that the combination of TRAIL and Mifepristone would kill cancer cells via apoptosis, because TRAIL is known to kill cancer cells by apoptosis, as taught by Bonavida et al, Yu et al, Gliniak et al, and because Mifepristone also kill cancer cells via apoptosis, as taught by Fathy El Etreby et al.

Applicant argues that a treatment that may work for one type of cancer, is often ineffective in other types of cancers. Applicant argues that the instant application teaches that not all prostate cancer cells are sensitive to TRAIL. Applicant argues that the instant specification teaches that certain androgen sensitive prostate cells, LNCaP, are not sensitive to Mifepristone at the levels used by Applicant, as shown in figure 1A, C. Applicant argues that the results of Gliniak and Koide use cancers that are not prostate cancers, and do not teach or suggest the use of TRAIL with another agent for treating prostate cancer. Applicant argues that Yu et al do not indicate how TRAIL may be used to treat prostate cancer cells that are not sensitive to TRAIL. Applicant argues that Koide and Fathy El Etreby do not teach how Mifepristone or other anti-progestins may be used to treat prostate cancer cells that are resistant to TRAIL.

Applicant argues that the prior art only provide an invitation to explore. There is no suggestion to use TRAIL with an antiprogestin that activates the TRAIL pathway. Applicant argues that although both TRAIL and Mifepristone have been used individually with some efficacy in treating prostate cancer, there is no indication that a

combination of TRAIL and Mifepristone would induce apoptosis in prostate cancer cells that are refractory to TRAIL alone.

This is not found to be persuasive. It is noted that the claims are not limited to a composition for treating prostate cancer. Further, because the composition comprising TRAIL and Mifepristone taught by the combined art is the same as the claimed composition, and thus one would have expected that the composition taught by the combined art would have the same characteristic and properties as the claimed composition, and could produce the same results concerning treating prostate cancer.

Further, it would have been obvious to package TRAIL and Mifepristone, such that Mifepristone is partially released prior to the release of TRAIL or both are released simultaneously, because such mode of operation is common in the art when a combination of drugs are used, to increase the effectiveness of the drugs.

With regards to the amounts of TRAIL or Mifepristone recited in claims 33-38, to determine optimum concentration of reactants is within the level of ordinary skill in the art. See In re Kronig, 190 USPQ 425.

Further, new claims 45-51 are drawn to the composition of TRAIL and an antiprogestin, which results in an increase in at least one death receptor, or at least one of DR4 or DR5 (claims 45-46), or an increase in activated caspase enzymes, wherein said activated caspases could be caspase-8 -7, -9 or -3 (claims 47-48), or an increase in truncated BID protein (claim 49), or in a reduction in mitochondrial function (claim 50), or an increase in apoptosome formation (claim 51).

The new claims are obvious, because the composition comprising TRAIL and Mifepristone taught by the combined art is the same as the claimed composition, and thus one would have expected that the composition taught by the combined art would have the same characteristic and properties as the claimed composition, and could produce an increase in at least one death receptor, or at least one of DR4 or DR5, or an increase in activated caspase enzymes, wherein said activated caspases could be caspase-8 -7, -9 or -3, or an increase in truncated BID protein, or a reduction in mitochondrial function, or an increase in apoptosome formation.

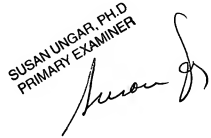
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



MINH TAM DAVIS

March 01, 2005